UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D.C. 20231
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/300,978	04/28/1999	LYNN E. SPITLER	204372000301	5058

25225 7590 07/02/2002

MORRISON & FOERSTER LLP
3811 VALLEY CENTRE DRIVE
SUITE 500
SAN DIEGO, CA 92130-2332

EXAMINER
GAMBEL, PHILLIP

ART UNIT	PAPER NUMBER
1644	22

DATE MAILED: 07/02/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/300978	Applicant(s) SPITLER
	Examiner GAMBEL	Art Unit 1644

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☑ Responsive to communication(s) filed on 4/10/02

2a)☐ This action is **FINAL**. 2b)☑ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☑ Claim(s) _____ is/are pending in the application. ~~1-12~~ 13, 15-16, 18-24

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☑ Claim(s) _____ is/are rejected. ~~1-12~~, 13, 15-16, 18-24

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a)☐ The translation of the foreign language provisional application has been received.

15)☑ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1)☑ Notice of References Cited (PTO-892)
2)☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3)☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____.
4)☐ Interview Summary (PTO-413) Paper No(s). _____.
5)☐ Notice of Informal Patent Application (PTO-152)
6)☐ Other:

DETAILED ACTION

1. Applicant's Replacement Brief on Appeal, filed 4/10/02 (Paper No. 20), is acknowledged.

Given applicant's definition of Tumor-associated antigen in Appendix B, this Office Action addresses applicant's reliance on this definition and assertion that the primary reference of Spitler refers to the use of a tumor associated antigen which is not found in normal tissue as the active ingredient in a vaccine.

Claims 13, 15, 16 and 18-24 are pending and being acted upon as they read on the PSMA.

Claims 1-12, 14 and 17 have been canceled previously.

2. The text of those sections of Title 35 USC not included in this Action can be found in a prior Action. This Office Action will be in response to applicant's arguments, filed 4/10/02 (Paper No. 20). The rejections of record can be found in the previous Office Actions (Paper Nos. 7/11).

3. Upon reconsideration of applicant's reliance on the disclosure on pages 8-9 of the specification as filed for the nucleic acid sequences encoding PSMA or PAP, the previous rejection under 35 U.S.C. 112, first paragraph, written description has been withdrawn.

4. Upon reconsideration of applicant's reliance on original claim 12 (versus the previous reliance on pages 4-5 and 17-19 of the specification), the previous rejection under U.S.C. 112, first paragraph, new matter with respect to claim 24, has been withdrawn.

The specification is objected to as failing to provide proper antecedent basis for the claimed subject matter. See 37 C.F.R. § 1.75(d)(1) and M.P.E.P. § 608.01(l). Correction of the following is required:

Applicant is required to amend the specification to provide proper antecedent basis for the recitation of claim 24, that is, "wherein said subject is afflicted with metastatic prostate and/or where said subject has been surgically treated to excise said tumor but is at risk for recurrence". .
It appears that the only support for claim 24 is original claim 12.

5. Upon reconsideration of the recitation of the current claims, the previous rejection under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-8 of U.S. Patent No. 5,925,362 has been withdrawn.

6. Claims 13, 15, 16 and 18-24 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Spitler (U.S. Patent No. 5,738,867 in view of Israeli et al. (U.S. Patent No. 5,538,866), Horoszewicz (U.S. Patent No. 5,162,504), Andriole et al. (Ann. Rev. Med. 42: 9-15, 1991) and in view of art acknowledged methods of delivering antigens of interest to stimulate antitumor responses, as disclosed on pages 10-19 of the instant specification and in further evidence of McCarley et al. (Seminars in Surgical Oncology 5:293-301, 1989).

Spitler teaches methods of delivering antitumor vaccines with tumor associated antigens, including prostate antigens (see Summary of the Invention), as well as known methods of delivering said tumor associated antigens to stimulate antitumor responses, encompassed by the claimed invention (see entire document). Spitler teaches that patients with cancer may have the cancer surgically excised and the be given the subject tumor vaccines (see column 10, lines 39-47).

Spitler differs from the instant claimed methods by not disclosing a particular prostate antigen, nor the elected species PSMA per se.

Israeli et al. teach PSMA , including nucleic acids and methods of expressing said PSMA, as well as its expression on prostate tumors (see entire document, including Background of the Invention and Detailed Description of the Invention). Israeli et al. teach that the main metastatic site for prostatic tumor is the bone (column 23, paragraph 2).

Horoszewicz (U.S. Patent No. 5,162,504) teaches that there is a need for monoclonal antibodies which are prostate specific and which do not cross react with other tissue types (see column 6, paragraph 2 and provides for the monoclonal antibodies specific for prostatic tumor antigens and distinguishable from prior prostate antigens (see entire document, including Summary of the Invention and Claims). Horoszewicz further discloses that prostatic epithelium has limited distribution, does not carry out functions vital for the survival of a patient and has been shown to produce organ specific molecules (see column 3, paragraph 3). In addition, the evidence for the selective specificity for the 7E11-C5 for human prostatic epithelium was reinforced by consistently negative results of immunospecific staining of numerous fresh frozen sections from a wide range of human non-prostatic normal or malignant tissues (see column 24, paragraph 3 and Results).

Andriole et al. Review the diagnosis and treatment of prostate cancer and teach that surgical excision of the prostate is unsurpassed as a means of controlling organ-confined prostate cancer (see page 13, paragraph 2).

McCarley et al. teach that in prostate cancer, monoclonal antibodies prostate antigens are not usually tumor specific (See Abstract and page 298, column 2, paragraph 3 - page 299).

Pages 10-19 of the specification discloses the art known methods of delivering antigens, including tumor associated antigens, of interest to stimulate antitumor responses encompassed by the claimed methods.

Given the teachings of Israeli et al. and Horoszewicz that the PSMA / 7E11 specificity is a marker or antigen for prostate cancer; one of ordinary skill in the art at the time the invention was made would have been motivated to substitute the prostate tumor associated antigen PSMA into the methods of stimulating antitumor responses, as known and practiced in the prior art, as taught by Spitler and acknowledged by the specification as to treat prostate cancer. Given the tissue and tumor specificity of the PSMA / 7E11 specificity as well as immunogenicity as well as its advantages over previous prostate antigens taught by Israeli and Horoszewicz coupled with McCarley et al. teaching that in prostate cancer, monoclonal antibodies prostate antigens are not usually tumor specific (See Abstract and page 298, column 2, paragraph 3 - page 299); one of ordinary skill in the art at the time the invention was made would have been motivated to apply the PSMA prostate antigen in the methods of Spitler to elicit antitumor responses to prostate antigens. It would have been obvious to the ordinary artisan to use PSMA in patients with metastatic prostate tumors and/or patients who have had the prostate tumor removed surgically to elicit antitumor responses in order to treat said cancer patients. Again, Spitler teaches that patients with cancer may have the cancer surgically excised and the be given the subject tumor vaccines (see column 10, lines 39-47) and Andriole et al. teach that surgical excision of the prostate is unsurpassed as a means of controlling organ-confined prostate cancer (see page 13, paragraph 2). Also, it would have been obvious to the ordinary artisan to select portions, particularly extracellular portions of PSMA to stimulate antitumor responses. From the teachings of the references and known in the prior art; it was apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

7. Applicant's arguments, filed 4/10/02 (Paper No. 20), have been fully considered but are not found convincing essentially for the reasons of record and addressed above.

Applicant's arguments and the examiner's rebuttal are essentially the same as of record.

Additional references have been cited to counter applicant's assertions that Spitler's teaching of tumor associated antigens read on cancer unique antigens and do not read on prostate antigens such as PSMA. Again, Spitler does not use the term "unique" as asserted by applicant. Spitler does not use the term "tumor specific antigen". Spitler teaches "tumor associated antigens" and given the standard well known understanding of "tumor associated antigens", PSMA reads on Spitler's teaching of eliciting antitumor responses to prostate tumor associated antigens. Further, the antigens cited by Spitler are not unique to tumor tissue but fall into the well known understanding of tumor associated antigens, in contrast to applicant's assertions.

Additional references have been cited in the rejection under 35 USC 103 to further support the PSMA antigen as an antigen specific for prostate tissue, including prostate cancer and that vaccination for prostate antigens such as PSMA would have been combined with standard excision of the prostate tumor at the time the invention was made.

Given applicant's arguments concerning the primary reference employed in the obviousness rejection of record, the examiner requested for a definition of tumor associated antigen in the context of their arguments.

In response, applicant has provide for a definition of Tumor-associated antigen in Appendix B, which reads as follows.

Tumor-associated antigen: A molecule specifically or preferentially expressed by tumoral cells, but not, hardly, by normal cells. Such molecules can be used as vaccination targets to destroy the tumor.

It is noted that applicant provides this definition obtained from the Aventis website, however the examiner could not locate this particular definition at the Aventis website.

In turn, applicant's has apparently relied upon this definition to support previous assertions that the primary reference of Spitler refers to the use of a tumor associated antigen to an antigen which is not found in normal tissue as the active ingredient in a vaccine.

Applicant argues that the present invention represents a different approach from the art by relying upon uniquely tumor-associated antigens as active ingredients, the present invention employs antigens namely PSMA and PAP that are associated with the host prostate tissues, that is, the antigens are found in normal prostate in contrast to other tissues. Generally, these antigens are found both in the normal prostate and in malignant prostate tissue (see page 4, lines 11-22 of the instant specification). The invention takes advantage of the fact that the prostate is not an essential organ and thus an immune response which could include disruption of normal tissue is acceptable (see page 4, lines 11-22 of the instant specification).

Again, applicant has mischaracterized the term tumor-associated antigen as understood by one of ordinary skill in the art at the time the invention was made and the reference. Further, the application of applicant's submitted definition of tumor associated antigens in the context of prostate antigens also mischaracterizes the term tumor-associated antigen as understood by one of ordinary skill in the art at the time the invention was made and the reference.

The Illustrated Dictionary of Immunology (Cruse et al., CRC Press Boca Raton 1995) (page 302) defined tumor associated antigens as follows:

Tumor-associated antigens: Certain antigens designated as CA-125, CA-19-9 and CA195, among others may be linked to certain tumors such as lymphomas, carcinomas, sarcomas, and melanomas, but the immune response to these tumor-associated antigens is not sufficient to mount a successful cellular or humoral immune response against the neoplasms. Three classes of tumor-associated antigens have been described. Class 1 antigens are very specific for a certain neoplasms and are absent from normal cells. Class 2 antigens are found on related neoplasms from separate individuals. Class 3 antigens are found on malignant as well as normal cells, but show increase expression in the neoplastic cells. Assays of clinical values will be developed for class 2 antigens, since they are associated with multiple neoplasms and very infrequently are found in normal individuals.

Immunology, Second Edition (Kuby, W.H. Freeman and Company, New York, 1991) (see page 590, column 2 and page 613, column 2; Tumor-Associated Antigens and Tumor-Specific Antigens) defined tumor associated antigens as follows:

Tumor-associated antigens: cell-surface proteins that are present on tumor cells and normal cells.

Tumor-specific antigens: cell-surface proteins found on tumor cells not on normal cells.

The majority of tumor antigens are not unique to tumor cells but also are present on normal cells and are called tumor-associated antigens. These antigens may be expressed only on fetal cells but not on adult cells, or they may be antigens expressed at low levels on normal cells but at much higher levels by tumor cells. (page 590, column 2).

Fundamental Immunology, Second Edition (Paul, Ed, Raven Press, New York, 1989) (page 931, column 1, paragraph 1; Differentiation Antigens and Other Tumor-Associated Antigens) discloses that Some antigens expressed on tumor cells are also expressed on normal cells during at least some stage of differentiation markers. The extend to which these differentiation antigens are expressed by normal cells and tissued can vary from widespread expression to extreme restriction by a small clone of normal cells. Furthermore, the time during development when these markers are expressed on normal cells can vary considerably. Since none of these antigens is tumor specific, they are commonly referred to as "tumor-associated" antigens. These antigens represent a very diverse group of glycoproteins and glycolipids.

In discussing Diagnostic and Therapeutic Utility of Monoclonal Antibodies in Urologic Oncology, McCarley et al. (Seminars in Surgical Oncology 5:293-301, 1989) disclose that to date, monoclonal antibodies which are absolutely specific for cancer cells have not been found (page 293, column 2, paragraph 4).

Further, McCarley et al. disclose that in prostate cancer, monoclonal antibodies prostate antigens are not usually tumor specific (See Abstract and page 298, column 2, paragraph 3 - page 299).

Horoszewicz (U.S. Patent No. 5,162,504) teaches that there is a need for monoclonal antibodies which are prostate specific and which do not cross react with other tissue types (see column 6, paragraph 2 and provides for the monoclonal antibodies specific for prostatic tumor antigens and distinguishable from prior prostate antigens (see entire document, including Summary of the Invention and Claims). Horoszewicz further discloses that prostatic epithelium has limited distribution, does not carry out functions vital for the survival of a patient and has been shown to produce organ specific molecules (see column 3, paragraph 3). In addition, the evidence for the selective specificity for the 7E11-C5 for human prostatic epithelium was reinforced by consistently negative results of immunospecific staining of numerous fresh frozen sections from a wide range of human non-prostatic normal or malignant tissues (see column 24, paragraph 3 and Results).

In addition, applicant asserts that in sharp contrast to TAAs which are either not present or barely present in normal tissue, applicant asserts that it is clear from Spitler (U.S. Patent No. 5,738,867) cited in the obviousness rejection under 35 USC 103, that the TAAs contemplated therein were associated with tumors and not normal tissues, such as carcinoembryonic antigen and melanoma antigen, citing column 4, lines 7-10 of Spitler.

Here, Spitler discloses the TAAs of CO 17-1A and KS1/4, both of which are expressed on both tumor and normal tissues, in contrast to applicant's assertions

In the Background of the Invention on column 1, lines 37-52), Grauer et al. (U.S. Patent No. 5,250,297) discloses that certain antigens are expressed by both human tumor cells and normal cells. These antigens are accordingly referred to not as "tumor specific" but as "tumor-associated" antigens. The diagnostic and therapeutic value of such tumor-associated antigens generally results from the excess quantity of antigen expressed by tumor cells relative to normal cells and the in vivo selectivity of antibodies for antigens for antigens expressed by tumor cells over normal cells.

Grauer et al. goes on to disclose that only a limited number of tumor associated antigens are well characterized, including the KS1/4 specificity (column 1, lines 53-67).

Varki et al. (Cancer Research 44: 681-687, 1984) disclose that the monoclonal antibodies KS1/4 is reasonably specific for lung cancer cells since it binds strongly to tumor tissues but either failed to react or reacted weakly with a variety of normal tissues (see entire document, including Abstract, Results and Discussion).

Further, Spitler (U.S. Patent No. 5,738,867) discloses several representative tumor associated antigens, including those of particular interest, including CO-029 and GA733-2 (see column 3, paragraph 3), both of which are expressed on normal tissues to some degree.

For example, Linnenbach (U.S. Patent No. 5,185,254) discloses that the tumor associated antigen GA733 is expressed on human stomach adenocarcinoma cells and that antibodies that bind GA733 bind to a variety of tumors and to varying degrees to normal epithelial tissues (e.g. see the first paragraph of the Background of the Invention).

Linnenbach et al. (U.S. Patent No. 5,668,002) discloses that the tumor associated antigen CO-029 was found to be expressed on gastric, colon, rectal and pancreatic carcinomas but not on most normal tissues (Sela et al., Hybridoma 8: 481-491, 1989) (e.g. see the first paragraph of the Background of the Invention).

Sela et al. (Hybridoma 8: 481-491, 1989) discloses that the antibody CO-029 binds gastrointestinal tract tumor cell lines and restricted binding specificities to human tissues and tumors (see entire document, including page 482, lines 3-5 and pages 483, overlapping paragraph, Binding Specificity of Mab CO-029).

Therefore, applicant's assertions that tumor associated antigens as taught by the primary reference Spitler is limited to antigens specific or unique to tumor cells (e.g. tumor-specific antigens) as opposed to associated with tumor cells (e.g. tumor associated antigens) is clearly inconsistent with the art recognized understanding of tumor-associated antigens and is clearly inconsistent with the Examples set forth in the primary Spitler (U.S. Patent No. 5,738,867) reference.

Again, with respect to prostate tumor associated antigens, the following is noted.

McCarley et al. disclose that in prostate cancer, monoclonal antibodies prostate antigens are not usually tumor specific (See Abstract and page 298, column 2, paragraph 3 - page 299).

Horoszewicz (U.S. Patent No. 5,162,504) teaches that there is a need for monoclonal antibodies which are prostate specific and which do not cross react with other tissue types (see column 6, paragraph 2 and provides for the monoclonal antibodies specific for prostatic tumor antigens and distinguishable from prior prostate antigens (see entire document, including Summary of the Invention and Claims). Horoszewicz further discloses that prostatic epithelium has limited distribution, does not carry out functions vital for the survival of a patient and has been shown to produce organ specific molecules (see column 3, paragraph 3). In addition, the evidence for the selective specificity for the 7E11-C5 for human prostatic epithelium was reinforced by consistently negative results of immunospecific staining of numerous fresh frozen sections from a wide range of human non-prostatic normal or malignant tissues (see column 24, paragraph 3 and Results).

Given the teaching of Spitler for employing tumor associated antigens associated with prostate, it would have been a reasonable understanding by the ordinary artisan at the time the invention was made to employ prostate antigens such as PSMA which was weakly expressed on normal prostate epithelium but strongly expressed on malignant prostatic epithelium. In turn, this differential normal versus malignant expression of PSMA fits within the definition of tumor associated antigens as understood by one of ordinary skill in the art.

Applicant's arguments are not found persuasive.

8. No claim is allowed.

10. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Phillip Gambel whose telephone number is (703) 308-3997. The examiner can normally be reached Monday through Thursday from 7:30 am to 6:00 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (703) 308-3973. Any inquiry of a general nature or relating to the status of this application should be directed to the Technology Center 1600 receptionist whose telephone number is (703) 308-0196.

Papers related to this application may be submitted to Technology Center 1600 by facsimile transmission. Papers should be faxed to Technology Center 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center telephone number is (703) 305-3014.

Phillip Gambel, PhD.
Primary Examiner
Technology Center 1600
July 1, 2002

CHRISTINA CHAN
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600